

**Investigating Associations Between Early Life Stress, Neural Response to Reward, and Depression**

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Submitted to the Graduate Faculty of

The Kenneth P. Dietrich School of Arts & Sciences in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2020

UNIVERSITY OF PITTSBURGH  
DIETRICH SCHOOL OF ARTS AND SCIENCES

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# **Investigating Associations Between Early Life Stress, Neural Response to Reward, and Depression**

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University of Pittsburgh, 2020

The link between exposure to early life stress (ELS), such as child maltreatment, and the development of depression has been well-replicated. However, the mechanisms that underlie this connection remain poorly understood. One potential mechanism may be neural alterations in reward-related brain regions, such as the ventral striatum and sub-regions of the prefrontal cortex. Recent research indicates that exposure to child maltreatment is associated with aberrant reward-related brain activity. A separate body of work implicates similar reward-related neural alterations in the etiology and maintenance of depression. The current study investigated whether altered neural response to reward plays a mechanistic role in explaining the association between ELS and depression. Here, we examined associations between history of child maltreatment, depressive symptoms, and neural response to reward during a reward processing fMRI task in a sample of adult men ( $N = 165$ ; 30.5% White, 60.6% Black) who were a part of the Pittsburgh Youth Study (PYS), a longitudinal study examining the development of negative mental health outcomes. History of child maltreatment was assessed via referrals prior to age 18 from the Allegheny County's Office of Children, Youth, and Families. Neuroimaging data and self-reported depressive symptoms were collected in adulthood ( $M$  age = 32.64,  $SD$  age = 3.62). Child maltreatment significantly predicted greater depressive symptoms. Child maltreatment and depressive symptoms were, however, not significantly associated with altered neural response to reward. Findings from the current study suggest directions for future work probing characteristics of adversity (e.g., chronicity, timing), as well as specific factors likely to moderate neural responses to reward (e.g., reward phase, magnitude of gains).

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## **1.0 Introduction**

Early life stress (ELS) refers to the experience of single or multiple traumatic events during childhood or adolescence that result in frequent and/or prolonged activation of the body's stress response (Carr, Martins, Stingel, Lemgruber, & Juruena, 2013; Pechtel & Pizzagalli, 2011; Shonkoff, 2010). While ELS encompasses a wide array of experiences, one predominant form of ELS is child maltreatment, defined as physical or emotional neglect, or emotional, physical, or sexual abuse (Jaffee, 2017). In the United States, over 6 million children are referred to Child Protective Services each year for abuse and neglect, and the number of children who experience maltreatment is thought to be underestimated due to under-reporting (U.S. Department of Health & Human Services, 2016).

Exposure to ELS, such as child maltreatment, has been strongly linked to negative mental health outcomes in adulthood. The connection between ELS and major depressive disorder (MDD), in particular, has been well established (LeMoult et al., 2019; Li, D'arcy, & Meng, 2019). MDD is a mood disorder characterized by at least two weeks of persistently low mood or loss of pleasure/interest (American Psychiatric Association, 2013). Large, longitudinal, cohort studies have shown that childhood adversity exposure is strongly associated with depressive symptoms in adulthood (Björkenstam, Vinnerljung, & Hjern, 2017; Kisely et al., 2018). Indeed, those who experience ELS are twice as likely to develop MDD later in life compared to those without such exposure (Nanni, Uher, & Danese, 2012). There is also evidence indicating a dose-response relationship, such that those who have experienced multiple forms of ELS are increasingly likely to develop MDD with each additional exposure (Felitti et al., 1998). Moreover, ELS is associated with a more severe and chronic course of MDD (Carr et al., 2013; Chapman et al., 2004; Wiersma

et al., 2009), as well as poorer response and remission outcomes for the treatment of this disorder (Williams, Debattista, Duchemin, Schatzberg, & Nemeroff, 2016). Despite the well-replicated link between ELS and the onset and maintenance of MDD, the mechanisms by which ELS increases risk for MDD remain unclear.

Recent work highlights reward processing as a potential mechanism explaining the association between ELS and increased risk for MDD. Reward processing encompasses sensitivity to reward, anticipation of reward, and response to the receipt of reward (see Barch, Pagliaccio, & Luking, 2012 for review). Neurally, functional brain activation in the cortical-striatal circuit has been implicated in reward processing (Haber & Knutson, 2010), specifically in the ventral striatum (VS) and different sub-regions of the prefrontal cortex (PFC), including the medial PFC (mPFC) and orbital frontal cortex (OFC). Functional associations have also been noted in other regions within the cortical-striatal circuit (e.g. anterior cingulate cortex, dorsolateral PFC), in relation to mechanisms that facilitate reward processing such as working memory and conflict monitoring (Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008; Remijnse et al., 2009). However, the VS, mPFC, and OFC activate most consistently in response to reward processing. The VS, along with these different portions of the PFC, are responsive during the processing of both primary (e.g., food) and secondary (e.g., monetary) rewards (Frank & Claus, 2006; Haber & Knutson, 2010). Moreover, these various regions of the cortical-striatal circuit are influenced by the dopamine system. The VS and mPFC in particular are both affected by projections of midbrain dopamine neurons, and changes in dopamine function have been linked to altered neural response to reward in these areas (Haber & Knutson, 2010).

Critically, reward-related alterations in behavior and brain functioning play a key role in the development of MDD (Alloy, Olino, Freed, & Nusslock, 2016; Auerbach, Admon, &

Pizzagalli, 2015; Forbes & Dahl, 2012; Forbes, Shaw, & Dahl, 2007; Treadway & Zald, 2013). For instance, blunted activation in the VS during the anticipation and receipt of both monetary rewards and positive stimuli have been associated with MDD (Epstein et al., 2006; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005b; Smoski et al., 2009). Altered reactivity in PFC sub-regions have also been linked with MDD (Zhang, Chang, Guo, Zhang, & Wang, 2013), with many studies finding that adults (Keedwell, Andrew, Williams, Brammer, & Phillips, 2005a; Keedwell et al., 2005b) and adolescents (Forbes et al., 2009) with depression show increased mPFC activation. However, findings regarding the directionality of mPFC activation are inconsistent, as others have shown decreased reactivity in the mPFC in individuals with depression (Epstein et al., 2006; Forbes et al., 2006).

Recent research indicates that those exposed to ELS may similarly demonstrate reduced sensitivity to monetary rewards and altered activation in reward-related brain regions during reward processing (Novick et al., 2018; Weller & Fisher, 2013). For example, children without a history of maltreatment have been shown to respond more quickly to stimuli that were associated with an increased chance of winning a reward, while maltreated children did not demonstrate such response time differences (Guyer et al., 2006). Moreover, one epidemiological cohort study reported an association between ELS and alterations in reward-related brain regions, including hypoactivation in the VS (Boecker et al., 2014).

Connecting these different research findings, the current study aimed to investigate associations between ELS, depressive symptomatology, and reward-related activation in the cortical-striatal circuit. Given that current treatments for depression are often less effective for those with a history of ELS, such as child maltreatment (Nanni et al., 2012; Williams et al., 2016),

information about potential mechanisms could aid in identifying those at risk, implementing prevention measures, and improving treatment methods following ELS.

### **1.1 Early Life Stress Alters Reward-Related Processes and Brain Systems**

Across the course of development, the cortical-striatal circuit undergoes dramatic neurodevelopment. Importantly, given the protracted neurodevelopment of the structures within this circuit, these still-developing systems may be influenced by exposure to environmental stressors, such as ELS (Teicher et al., 2003; Teicher, Samson, Anderson, & Ohashi, 2016). Studies of non-human animals show that exposure to ELS significantly alters the dopamine system, behavioral responses to reward, and functional reactivity in regions within the cortical-striatal circuit (Ironside, Kumar, Kang, & Pizzagalli, 2018; Pechtel & Pizzagalli, 2011). For instance, in non-human animals (e.g. rats, marmoset monkeys), exposure to ELS, such as maternal separation and social isolation, leads to reduced expression of dopamine receptors and reduced dopamine transmission in the VS as well as blunted activation of the VS in response to reward (Anisman & Matheson, 2005; Pizzagalli, 2014; Pryce, Dettling, Spengler, Spaete, & Feldon, 2004). Mice exposed to chronic social defeat, a form of chronic stress, also show increased dopamine receptor expression in the mPFC (Bagalkot et al., 2015), suggesting that ELS may lead to hyperactivation in this region.

Studies sampling both human adults and youth exposed to ELS similarly report impaired responses to reward and neural alterations in reward-related brain regions. For instance, in a sample of adults with and without a history of childhood sexual abuse, previously abused participants showed reduced accuracy in a reward learning task, irrespective of MDD history (Pechtel &

Pizzagalli, 2013). Further, a growing body of research finds that exposure to child maltreatment is specifically associated with impaired functional activation in the VS during reward processing tasks. One study of young adults found that, compared to non-maltreated controls, participants who experienced child maltreatment before the age of 14 showed reduced behavioral responses to reward-predicting cues and decreased activity to reward cues in the left basal ganglia, an area including the VS, during the monetary incentive delay task (MID) (Dillon et al., 2009). In a separate sample of adults, who were part of a longitudinal study of youth followed since kindergarten, those with greater levels of ELS demonstrated lower activity in the VS during the processing of monetary rewards (Hanson, Albert, et al., 2015).

Prior work examining associations between ELS and reward-related brain activity has relied largely on self-reported assessments of child maltreatment. Given that self-report measures are susceptible to reporting bias that may influence results, it is important to examine the link between ELS and altered brain activity using more objective measures of exposure to child maltreatment. For instance, one notable study of previously institutionalized adolescents who experienced severe psychosocial deprivation and neglect found that these adolescents demonstrated diminished VS activity during a reward processing task relative to the control group (Mehta et al., 2010). While these findings suggest strong connections between ELS and blunted reward-related VS activity, associations with depression were not investigated.

More recent research has begun to examine associations among ELS, functional activation in reward-related brain regions, and depression. One finding from a sample of youth aged 6 to 15 found that, compared to healthy controls, institutionalized youth demonstrated decreased VS reactivity during the passive viewing of emotional faces (Goff et al., 2013). This hypoactivation of the VS during the task was associated with greater symptoms of depression. While this finding

suggests that ELS exposure may impair neural activation in the VS, this work did not examine VS activity in the context of reward processing, nor formally test whether differences in VS reactivity explained ELS-related increases in depression.

Another group reported that adults with MDD, but not healthy controls, demonstrated a positive correlation between perceived levels of recent and chronic life stress and greater mPFC activation during an acute stress induction when processing rewards (Kumar et al., 2015). This finding shows an interesting association between stress and depression. However, since individuals diagnosed with depression have been shown to demonstrate altered neural response to reward, inferences regarding the influence of more chronic ELS on changes in brain activity are less clear. In a promising study examining adolescents aged 11 to 15, greater levels of emotional neglect predicted lower reward-related VS activity two years later, which partially mediated the association between emotional neglect and later depressive symptoms (Hanson, Hariri, & Williamson, 2015). However, they did not examine alterations in other reward-related brain regions, such as the mPFC or OFC. Moreover, both of these studies used retrospective, self-report measures of stress exposure.

The sub-regions of the PFC play critical roles in reward processing (Frank & Claus, 2006; Haber & Knutson, 2010). Despite this fact, few studies have investigated relations between ELS and neural response to reward in these regions. However, there are notable exceptions. One study of adolescent girls examined the relation between the number of years of household receipt of public assistance from ages 5 to 16, a potential proxy for ELS, and activation in the mPFC. The number of years of household receipt of public assistance was positively associated with mPFC activation during the anticipation of reward. This increased mPFC activity mediated the relation between socioeconomic disadvantage and symptoms of depression at age 16 (Romens et al., 2016).

This study provides preliminary evidence for increased reward-related activation in the mPFC following ELS. Nevertheless, it remains important to test whether other forms of ELS, such as child maltreatment, are associated with similar mPFC alterations. Interestingly, increased reward-related functional connectivity between the VS and mPFC has been reported in young adults with a self-reported history of child maltreatment who also reported greater levels of recent life stress, and this pattern of connectivity was associated with greater depressive symptoms (Hanson, Knodt, Brigidi, & Hariri, 2018). These findings point to a potential link between ELS exposure, increased reward-related mPFC reactivity, and later depression.

Limited work to date has assessed the associations between 1) child maltreatment, 2) neural response to reward throughout the cortical-striatal circuit (including the VS, mPFC, and OFC), and 3) depressive symptomatology in a full mediation model. This work is essential for understanding how child maltreatment impacts the reward circuit, and how these neural changes may in turn increase risk for future depression.

## **1.2 Depression, Reward Processing, and the Brain**

One of the core symptoms used to classify MDD is reduced motivation to pursue rewards (American Psychiatric Association, 2013). Independent of ELS, a host of studies indicate that individuals with MDD demonstrate impaired reward processing and altered neural functioning during reward processing tasks. Behaviorally, healthy adults with greater depressive symptoms have failed to demonstrate a preference for stimuli that predict reward during a signal-detection task (Pizzagalli, Jahn, & O'Shea, 2005). Adults diagnosed with MDD similarly show significantly

reduced responsiveness to rewards compared to healthy controls (Pizzagalli, Iosifescu, Hallet, Ratner, & Fava, 2008). Importantly, impaired reward processing has been shown to predict the onset of MDD. One longitudinal study found that boys (aged 10-11) with depressive symptoms failed to distinguish between high or low reward magnitudes under conditions of high probability of receiving reward (Forbes et al., 2007). In this same study, low frequency of choosing the high reward magnitude under the high probability condition predicted greater depressive symptoms and the development of depression one year later. Interestingly, blunted response to rewards even predicts persistent MDD following 8 weeks of antidepressant treatment (Vrieze et al., 2013).

Neurally, meta-analyses have found that, across the lifespan, MDD is characterized by disrupted activity within the cortical-striatal circuit during reward processing tasks (Groenewold, Opmeer, de Jonge, Aleman, & Costafreda, 2013; Zhang et al., 2013). Findings in both adult and youth samples suggest reduced reward-related activity in the VS in relation to depression. For instance, reduced activation in the VS during monetary gains compared to losses have been linked with severity of depression (Satterthwaite et al., 2015). Unmedicated adults with MDD have also shown significantly decreased responses to monetary gains in the left VS during both the anticipation and outcome of rewards in the MID task, compared to healthy controls (Pizzagalli et al., 2009). Comparable results have been found in adults with remitted MDD, who demonstrated blunted neural signal to reward feedback in an area associated with VS activity (Whitton et al., 2016). Lessened VS activation during the anticipation and outcome of reward has similarly been found in a sample of adolescents with MDD when compared to healthy adolescents (Forbes et al., 2009).

Heightened reactivity in regions of the PFC, specifically the mPFC, have been reported in relation to depression (Zhang et al., 2013). For instance, adults with depression show increased



mPFC activity in response to pleasant stimuli (Keedwell et al., 2005a, 2005b). Of note, the sample sizes for these studies were small (12 adults with MDD in the former, and 12 adults with MDD and 12 healthy controls in the latter) and they did not examine reward-related reactivity in the mPFC. However, one study of 78 adolescents similarly found that, compared to healthy controls, adolescents diagnosed with depression demonstrate heightened mPFC activity during the outcome phase of a reward processing task (Forbes et al., 2009). Importantly, results regarding the OFC are not perfectly uniform. One group found that adults with depression exhibited increased OFC activation during the “reward selection” phase of a monetary reward task (Smoski et al., 2009). Conversely, two other studies by the same group found that adults with depression had reduced activation in the right OFC when anticipating monetary rewards (Smoski, Rittenberg, & Dichter, 2011), and hypoactivation in the OFC during the outcome phase of the task in adults with remitted depression (Dichter, Kozink, McClernon, & Smoski, 2012). While the sample sizes in these studies were small (ranging from 9 to 19 adults with MDD, and 13 to 19 healthy controls), these results suggest altered reward-related reactivity in sub-regions of the PFC as a key feature of depression.

Overall, findings from both adult and youth samples demonstrate links between depression, impaired reward processing behaviorally, and blunted activation in VS in response to rewards. However, it remains important to investigate different sub-regions of the PFC, such as the mPFC and OFC, in relation to reward processing in depression. Given the well-established association between ELS and MDD, investigating functional alterations within the cortical-striatal circuit during reward processing may be important for elucidating this relation.

### 1.3 The Present Study

The current study used a well-validated fMRI reward processing task to evaluate neural responses to monetary gains vs. losses in a sample of adults with and without a history of child maltreatment. The four aims of the current study were to: 1) investigate whether ELS was related to depressive symptoms, 2) examine the association between ELS and reward-related reactivity in the cortical-striatal circuit, 3) examine the links between neural activity in this reward circuit and depressive symptoms, and 4) investigate the indirect effect of the reactivity in these reward-related regions on the association between ELS and depressive symptoms. The corresponding hypotheses were as follows (as depicted in Figure 1):

1. Exposure to child maltreatment would be associated with greater depressive symptoms.
2. Exposure to child maltreatment would be related to neural alterations in reward circuitry during the reward processing task, such as reduced activation in the VS and OFC as well as increased mPFC reactivity.
3. Alterations in neural response to reward, such as blunted VS activation and altered reactivity within the sub-regions of the PFC, would predict greater depressive symptoms.
4. Alterations in neural response to reward would statistically mediate, or explain, the association between ELS and depression. In other words, there would be an indirect effect of altered activation within the cortical-striatal circuit on the relation between exposure to child maltreatment and greater depressive symptoms.

If all four hypotheses were supported, the current study would provide evidence for altered neural response to reward as one potential mechanism that may explain the connection between ELS and depression.

## **2.0 Methods**

### **2.1 Participants**

The current project conducted a secondary data analysis of behavioral and neuroimaging data collected from the Pittsburgh Youth Study (PYS). PYS is a longitudinal study that initially recruited an urban community sample of 1,517 elementary school boys ranging from the ages of 6 to 13 (Loeber, Farrington, Stouthamer-Loeber, & Van Kammen, 1998). Participants were followed into adulthood and, along with their primary caregivers, completed repeated longitudinal assessments aimed at capturing potential risk factors for the onset, frequency, severity, and extinction of mental health problems. During a recent assessment (in 2010), a subsample of the participants ( $N = 205$ ) completed self-report measures and an fMRI scan. Participants who completed the neuroimaging sub-study were not significantly different from the full study on screening variables (including family socioeconomic status, number of biological parents in the home, and parent- and early teacher-reported behavioral problems, all  $p$ 's  $> 0.1$ ). Of this subsample, 30 participants were excluded for excessive movement, 1 participant was excluded due to the detection of a serious MRI anatomical abnormality, and 9 participants were excluded due to loss of task-based behavioral data in the fMRI scanner. Participants with usable fMRI data were included in the final sample ( $N = 165$ ; mean age at scan =  $32.64 \pm 3.62$ ; range = 26.45 – 40.82 years; 30.5% White, 60.6% Black).

## **2.2 Procedures**

The Pittsburgh Youth Study is a longitudinal investigation that aims to document the development of externalizing and internalizing disorders from childhood to adulthood and identify potential risk factors for such problems. This study has been written about extensively and is briefly discussed here (see Loeber et al., 1998 for more details). At the onset of the study in 1987-1988, three cohorts comprised of 503 first grade boys, 508 fourth grade boys, and 506 seventh grade boys were randomly selected to participate from Pittsburgh public schools. Over half of the participants were Black, while the remainder were mostly White. About two-fifths of the original sample were from families on welfare, and about two-fifths lived with a single parent. Researchers collected self-report, school, and archival court data. The assessments pertained to a wide range of risk and protective factors across various contexts, including at the individual, family, peer, school, and neighborhood levels. The measures assessed mental health problems that encompassed both externalizing and internalizing symptoms. The youngest cohort was assessed from ages 6 to 19, and at ages 25 and 28; the middle cohort from ages 9 to 13, and at age 23; the oldest cohort from ages 13 to 25, and at age 35. Over the course of the study, the full PYS has maintained a high retention rate (mean = 91%).

## **2.3 Measures**

### **2.3.1 Early Life Stress**

Official state service records from the Allegheny County's Office of Children, Youth, and Families (CYF) were used to assess exposure to child maltreatment. The current study used any CYF referrals involving the participant directly. The records included referrals reported from the participant's date of birth to the age of 18. The Maltreatment Classification System was used to describe different types of maltreatment (Barnett, Manly, & Cicchetti, 1993). The types of maltreatment included: physical abuse; sexual abuse; emotional abuse; physical neglect - failure to provide, or failure to meet a child's need for food, clothing, shelter, medical care, and adequate hygiene; physical neglect - lack of supervision, or leaving a child unattended or in the care of an inadequate caregiver (endangering a child); moral/legal/educational maltreatment, or a child being exposed to illegal activities, a child's involvement in illegal activities as a result of lack of adult intervention or encouragement or coercion by an adult, or failure to provide for a child's adequate education. This study categorized participants into two groups: those exposed to any type of child maltreatment (e.g., physical abuse; emotional abuse) and those without a history of child maltreatment. Participants in the maltreated group had at least one CYF referral, while participants in the non-maltreated group did not have any referrals. The final sample included 40 participants in the maltreated group and 125 participants in the non-maltreated group.

### **2.3.2 Depressive Symptomatology**

The Depression, Anxiety, and Stress Scales (DASS) is a widely used screening measure used to assess symptoms of depression, anxiety, and stress in community settings (Lovibond & Lovibond, 1995). The DASS is a set of three, 7-item self-report scales (21-items total) used to measure depression, anxiety, and stress, respectively. The current study used the depression scale to assess depressive symptoms over the past week. The 7-item depression scale is designed to assess dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/ involvement, anhedonia, and inertia. Each item is scored on a scale from 0 (“did not apply to me at all”) to 3 (“applied to me very much”). Total scores for the depression scale were calculated for each participant. Total depression DASS scores are interpreted as follows: 0-9 = normal, 10-13 = mild depression, 14-20 = moderate depression, 21-27 = severe depression, and total scores above 28 = extremely severe depression (Lovibond & Lovibond, 1995). To calculate each participant’s total score, the sum of each item was taken and the total was then multiplied by 2, with a minimum potential total score of 0 and maximum potential total score of 42. This is consistent with past published reports using the DASS.

### **2.3.3 fMRI Reward Processing Task**

A well-validated event-related card guessing task was used to probe reward activity in the brain (shown in Figure 2). This paradigm is one of the most commonly deployed fMRI reward processing tasks and has been shown to reliably activate reward circuitry (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000). Of note, the design of the reward processing task did not allow for the separation of reward anticipation and receipt of reward. Participants were told that the goal of the

card guessing game was to win as much money as possible. They were told that if they guessed correctly, they would win money and if they guess incorrectly, they would lose money. During the task, participants were asked to guess the number on the back of a card. Participants were told that the number on the back of each card could range from 1 to 9, and that they must guess whether the number is more or less than 5 by pressing one of two buttons on a response box. They were then presented with the actual number, followed by one of four feedback screens: a big upward green arrow showing that they won \$2.00; a small upward green arrow showing that they won \$0.20; a big downward red arrow showing that they lost \$1.00; a small downward red arrow showing that they lost \$0.10. For each trial of the task, participants were first presented with a decision card for 2.25 seconds, in which they had to guess via button press whether the value of the subsequent card, with a possible value of 1 to 9, will be greater or less than 5. The actual numerical value of the card was then presented for 0.75 seconds. Participants then received feedback for 0.75 seconds. Finally, a blank card was presented for a jittered inter-trial interval (mean = 5.2 seconds). Participants practiced the task before entering the scanner, and then completed 4 runs of the task lasting 4 minutes and 10 seconds each. Each run contained a total of 10 trials per condition. While participants were told that their performance during the task determined a monetary reward upon completion, the trial outcomes were predetermined and presented in a fixed, pseudorandom order. Of note, due to these fixed outcomes, we did not find differences in task performance between the maltreated and non-maltreated groups. The participants received \$20 in “winnings” after completing the task in the scanner. The current study compared neural activation in response to all win trials vs. all loss trials.



### **2.3.3.1 fMRI Data Acquisition**

Scanning took place on a Siemens 3T Magnetom TIM Trio magnet at the University of Pittsburgh's Magnetic Resonance Research Center. Multiple types of images were acquired during the scanning session, including structural (anatomical) images and task-based functional scans. A high-resolution T1-weighted, anatomical image covering the entire brain was acquired using an axial 3D MPRAGE (magnetization prepared rapid acquisition gradient echo) sequence parallel to the AC-PC line (TE/TI/TR = 3.29 ms/900 ms/2200 ms, flip angle = 9°, 1mm<sup>3</sup> voxel, 192 axial slices, matrix size = 256 × 192). Following the structural scan, the reward processing (fMRI) task was administered in the scanner. Functional images were acquired using a gradient echo EPI sequence that covered 37 AC/PC aligned axial slices containing the cerebrum and most of the cerebellum with the following parameters: TR/TE = 2000/28 ms, field of view (FOV) = 200 × 200, matrix = 64 × 64, flip angle=90°; 3.1mm<sup>3</sup>, 0mm gap.

### **2.3.3.2 fMRI Data Preprocessing and Restricted Voxel-Wise Analysis**

Pre-processing and analysis of imaging data were conducted using Analysis of Functional Neuroimages (AFNI; <http://afni.nimh.nih.gov>; Cox, 1996). Individual subject data were realigned to the first volume in the time series, high-pass filtered, percent signal change normalized, aligned to individual subject high-resolution structural images, spatially smoothed using a Gaussian filter set at 6-mm full-width at half-maximum, and then analyzed using a general linear model (GLM). Our GLM included separate regressors for each feedback type (small positive, small negative, large positive, large negative) convolving a (canonical) gamma variate hemodynamic response function. These first-level GLMs included nuisance covariates of the second-order polynomial used to model the baseline and slow signal drift, six motion estimate covariates, and binary flags corresponding to neuroimaging frames with excessive motion (>2mm). Participants with >20% of

total frames censored due to motion were excluded from all analyses ( $n = 30$ ). Structural images were then normalized to a standard stereotactic space (Montreal Neurological Institute template) using a non-linear diffeomorphic registration algorithm (AFNI's 3dQwarp). The resulting warps were applied to all functional data, re-sampled functional data to  $2\text{mm}^3$ .

Second-level (main-effect) neuroimaging GLMs were then constructed using mixed effects analysis, with subjects as a random factor. Of note, these analyses were restricted to brain areas previously implicated in reward processing using a mask derived from Neurosynth (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). In brief, Neurosynth (neurosynth.org), is an automated brain-mapping application that uses text-mining, meta-analysis, and machine-learning techniques to generate a large database of mappings between neural and behavioral/cognitive states. Using a Bayesian classifier, Neurosynth is able to identify brain areas connected with the terms employed in a published manuscript. Here, we focused on the term “reward” from Neurosynth's past study database. At the onset of this project, nine-hundred and twenty-two studies in the Neurosynth database consistently used the term “reward.” These studies were used to generate a reward mask to limit the neuroimaging search space (total number of  $2\text{mm}^3$  voxels in mask = 12,969).

Within this restricted search space, a voxel-wise between groups t-test was run comparing maltreated versus non-maltreated participants, for positive > negative feedback fMRI parameter estimates. This contrast was selected to assess overall neural response to monetary gains vs. losses. To correct for multiple comparisons, AFNI's 3dClustSim was deployed using cluster-size thresholding based on Monte Carlo simulation and new, mixed-model (non-Gaussian) autocorrelation functions used an initial, uncorrected statistical threshold of  $p < .01$  (Cox, Chen, Glen, Reynolds, & Taylor, 2017). Based on this threshold, the number of comparisons in the mask, and

the smoothness of the imaging data, a minimum cluster size of 161 was determined for a given cluster effect to have a corrected  $p \leq .05$ . For any regions above this threshold, the mean parameter estimates would be extracted by averaging across every voxel in each regional cluster and used in subsequent analyses.

### 3.0 Analytic Plan

The present study aimed to test: 1) the association between ELS and depression, 2) whether ELS is related to cluster activation within the reward mask, 3) whether such cluster activation is related to depressive symptoms, and if so, 4) the indirect effect of cluster activation within the reward mask on the relation between ELS and depressive symptoms. Study aims were tested using multiple regression conducted in SPSS Version 26 (IBM Corp., 2019). Age and race were considered as covariates in all analyses. Significance level was set to  $p < 0.05$  for each of these models.

The first linear regression model examined whether having CYF referrals or not (X) was associated with depression DASS scores (Y) (Hypothesis 1; path c). The second linear regression model examined whether having CYF referrals (X) was related to cluster activation within the reward mask (Y) (Hypothesis 2; path a). The third linear regression model tested whether cluster activation in the mask was associated with depression DASS scores (Y) (Hypothesis 3; path b). If path a (Hypothesis 2) and path b (Hypothesis 3) demonstrate significant associations, we planned on testing whether the observed association between having CYF referrals (X) and depression DASS scores (Y) would be statistically mediated by reactivity in any significant clusters (M) (Hypothesis 4; path c'). The formal mediation analyses would be conducted using SPSS PROCESS macro using a nonparametric bootstrapping approach with 5,000 bootstrap resamples and 95% confidence intervals for indirect (a X b) effects (Preacher & Hayes, 2008; Hayes, 2009; Hayes 2013). In order to conduct a mediation analyses, a significant a-path (Hypothesis 1) and a significant b-path (Hypothesis 2) are required (Hayes, 2018). Without such significant paths, it is

not possible to meaningfully interpret the presence of an indirect effect that may result from a mediation analysis.

## **4.0 Results**

### **4.1 Descriptive Statistics**

The means, standard deviations, and comparison statistics for study variables are presented in Table 1. A chi-square test did not reveal significant differences in race between the maltreated and non-maltreated group,  $\chi^2(1) = 0.017, p = 0.898$ . An independent samples t-test did not reveal significant differences in age between the two groups,  $t(163) = -0.466, p = 0.64$ .

### **4.2 Early Life Stress and Depressive Symptoms**

A multiple regression analysis showed that, after controlling for age and race, child maltreatment significantly predicted depression DASS scores ( $\beta = 0.158, SE = 6.34, p = 0.044$ ; Figure 3). These results indicate that exposure to ELS is significantly associated with greater depressive symptoms.

### **4.3 Early Life Stress and Neural Response to Reward**

In contrast to our predictions, the voxel-wise group t-test did not find significant regions above the minimum cluster size of 161 for the contrast Win > Loss. The largest cluster that resulted from this analysis was a cluster in the OFC, with a cluster size of 54 (Table 2; Figure 4). As an exploratory analysis, we conducted a multiple regression examining the relation between ELS and

the mean parameter estimates in the OFC cluster for the contrast Win > Loss. After controlling for age and race, child maltreatment was significantly associated with increased OFC activation for the contrast Win > Loss ( $\beta = 0.242$ ,  $SE = 0.09$ ,  $p = 0.002$ ; Figure 5).

#### **4.4 Depression and OFC Neural Responses to Reward**

To thoroughly probe group neural differences, we also conducted an exploratory multiple regression analysis to test whether activation in our OFC cluster for the contrast Win > Loss was associated with depressive symptoms. After controlling for age and race, the association between OFC activation for the contrast Win > Loss and depression DASS scores was not significant ( $\beta = 0.06$ ,  $SE = 6.41$ ,  $p = 0.452$ ).

Due to the lack of a significant association between the OFC cluster activation for the contrast Win > Loss and depressive symptoms, we did not conduct an exploratory mediation analysis to examine whether there would be an indirect effect of activation in the OFC cluster on the relation between ELS and depression.

## **5.0 Discussion**

### **5.1 Summary**

The present study investigated whether child maltreatment impacted neural circuitry connected to reward processing, whether these potential alterations were related to depression, and whether these neural alterations could begin to explain links between child maltreatment and depression. Although we replicated past behavioral findings showing that exposure to child maltreatment was associated with greater depressive symptoms, we did not find support for our predictions regarding the associations between ELS, the brain, and depression. We did not find significant associations between child maltreatment and altered activity in reward-related neural circuitry (e.g., VS; portions of the PFC). While an exploratory analysis indicated that ELS exposure was associated with increased activation in a small OFC cluster, this finding did not meet formal criteria for statistical significance. Additionally, we did not find that these brain differences related to depressive symptoms. Taken together, we do not have evidence to support the notion of altered neural response to reward in the VS and sub-regions of the PFC as a potential mechanism that explains the association between ELS and depression.

### **5.2 ELS and Reward Processing**

Previous research finds that exposure to ELS significantly alters neural functioning in brain regions related to reward; however, the present study did not replicate this finding. Interestingly,



our exploratory analysis found a suggestive link between child maltreatment and increased OFC activation. While we cannot formally draw conclusions from this finding, as the cluster size was below the threshold needed to meet significance, this may point to the OFC as a region that may be particularly sensitive to ELS. For instance, recent work has found that ELS is associated with structural differences in this region. Physically abused children were found to have smaller OFC volumes compared to their non-abused counterparts, and smaller OFC volumes related to impaired behavioral functioning (Hanson et al., 2010). Similarly, compared to a group of non-maltreated children, a group of children exposed to any type of maltreatment demonstrated reduced grey matter in the OFC (De Brito et al., 2013). Given that ELS has been linked to structural differences in the OFC, and that such differences have been associated with impairments in behavioral functioning, it remains important to continue examining how alterations in OFC neural activity relate to ELS and behavioral functioning, such as reward processing.

Our inability to detect significant associations between child maltreatment and reward related brain activity may be due to 1) differential responses as a function of reward phase, 2) differential responses as a function of reward magnitude, and 3) the varied operationalization of ELS across the literature. First, we examined overall neural response to reward. However, reward processing is a complicated construct comprised of different phases (Knutson, Fong, Adams, Varner, & Hommer, 2001; Smith & Delgado, 2015). Reward processing is commonly distinguished into two phases: a) reward anticipation, or the preparation to make a response to a stimulus that may potentially result in a reward, and b) reward outcome, or the receipt of a reward. Individuals exposed to ELS may have differential associations with each of these separate components. In particular, individuals with ELS exposure have been shown to demonstrate altered neural activation during reward anticipation, but do not tend to show neural differences in response

to the receipt of reward. For instance, adolescent adoptees with early institutional deprivation demonstrated blunted neural response in the VS during the anticipation of reward in the MID task (Mehta et al., 2010). Adolescents with a history of emotional neglect also showed diminished VS activation during the anticipation of rewards (Hanson, Hariri, et al., 2015). This pattern of results has also been replicated in adults with a history of early adversity (Boecker et al., 2014; Dillon et al., 2009). The task used in the current study did not allow for the separation between reward anticipation and outcome, which may have made it difficult to detect reward-related neural differences between the maltreated vs. non-maltreated groups. It may be that neural differences exist during the anticipation of reward for individuals with a history of maltreatment, but our ability to detect such differences in the neural signal during reward anticipation may have been obscured by a lack of neural differences during reward outcome. Future research should use reward processing tasks that allow for a distinction between reward anticipation and outcome. Evidence from prior work suggests that adversity exposed samples would demonstrate reduced activation in the VS in response to reward anticipation, but not to the receipt of reward. However, the impact of ELS on neural response to reward anticipation versus outcome in the sub-regions of the PFC remains underexplored.

Second, evidence from previous research on the influence of ELS on reward circuitry may point to the magnitude of reward as another important factor to consider. When comparing adolescent adoptees exposed to institutionalization to healthy controls, Mehta and colleagues (2010) found that the control group showed increased activation in the VS and caudate nucleus in response to reward magnitude while the adoptees did not. Importantly, this difference was only found in response to large amounts of reward, as there were no significant differences between the groups in response to small amounts of reward. Behavioral studies mirror this finding, showing

that non-maltreated children respond quickly as the chance of winning increases, while maltreated children do demonstrate this difference (Guyer et al., 2006). In the current study, we aimed to capture robust activation within the reward circuit by combining small and large magnitudes of monetary gain, as well as small and large magnitudes of losses, and comparing neural response to all win trials vs. all loss trials. However, it may be that individuals exposed to ELS respond differently as the amount at stake changes. We aim to investigate this in future iterations of this project.

Finally, our null findings may be in part due to critical differences in how ELS is operationalized in the literature. The ways in which ELS is defined varies greatly across studies. Some studies use institutionalization (Goff et al., 2013; Mehta et al., 2010), which is a unique but also extreme experience of deprivation. Other studies use poverty or socio-economic disadvantage (Romens et al., 2016), which may be accompanied by a host of other stressors and environmental challenges. Studies also use self-report questionnaires aimed at assessing life stress and adverse events that exclude trauma (Kamkar, Lewis, van den Bos, & Morton, 2017; Kumar et al., 2018). Even though many other studies conceptualize ELS using child maltreatment, the type of exposure varies greatly between each study. Most studies tend to focus on just one type of abuse, such as sexual abuse (Pechtel & Pizzagalli, 2013) or emotional neglect (Hanson, Hariri, et al., 2015). While we believe it would be useful to examine specific types of abuse, our sample size does not allow for this.

Thinking about ELS, most past studies have not examined how the timing, duration, or severity of the exposure, regardless of how it is defined, impacts neural functioning. This may be another important consideration, as different types of exposures may have a more significant impact on later outcomes when experienced during a specific developmental time period (Cowell,

Cicchetti, Rogosch, & Toth, 2015; Gunnar & Quevedo, 2006; Manly, Kim, Rogosch, & Cicchetti, 2001; Paul & Eckenrode, 2015; Teicher & Samson, 2013). For instance, Hanson and colleagues (2015) found that adults who experienced childhood stress early in development (kindergarten to grade 3), but not later in development (grades 4 to 7 and grades 8 to 12), exhibited blunted VS activity during reward processing. It may be that child maltreatment experienced during a specific time window may impact neurodevelopment, while similar exposures experienced at a different time period may not influence neurodevelopment in the same way. The lack of consideration for the developmental timing of ELS, as well as differences in how ELS is defined and measured across studies, may make it difficult to replicate or generalize findings. In terms of accounting for developmental timing of ELS, future work should measure age and duration of each exposure. Regarding the operationalization of ELS, it would be important to replicate research that defines ELS in the same way.

### **5.3 Depression and Neural Response to Reward**

VS deactivation during reward processing has widely been reported in individuals with depression, and this has been supported by meta-analyses (Keren et al., 2018; Zhang, Chang, Guo, Zhang, & Wang, 2013). In terms of the sub-regions of the PFC, there have been a number of inconsistent findings regarding the directionality of the associations between these regions and depression. For instance, some studies indicate that individuals with depression demonstrate increased activation in the OFC and mPFC (Forbes et al., 2009; Smoski et al., 2009). However, others have found the opposite association, particularly in the OFC (Dichter et al., 2012; Smoski et al., 2011). A recent meta-analysis (Ng, Alloy, & Smith, 2018) highlights key issues across this

literature that may be contributing to these discrepant findings. Such problems include limited statistical power, PFC susceptibility to artifacts, and lack of agreement regarding the anatomical boundaries of PFC subregions. Ng and colleagues also found that many previous meta-analyses use inadequate statistical approaches that may have increased false positives among clusters. In their work, they conducted a meta-analysis following new and more stringent recommended statistical guidelines. While the authors did not report significant alterations in the mPFC in individuals with depression, they found that MDD is characterized by both hypoactivation in the VS and hyperactivation in the OFC. Although we did not find any significant associations between neural alterations in the brain and depressive symptoms, our exploratory analyses found that child maltreatment was correlated with increased activation in a modestly sized OFC cluster. While this was not formally significant, this may point to hyperactivation in the OFC as a potential feature to investigate more closely. For instance, future work could use reward processing tasks that reliably elicit OFC reactivity, such as reversal learning tasks. Moreover, future research could use different analytic techniques for fMRI data, such as psychophysiological interaction (PPI), to elucidate how regions within reward circuitry (including the OFC) are coupled.

Similar to findings with adversity exposed individuals, neuroimaging findings in depressed samples also indicate differential associations based on reward magnitudes, as well as reward anticipation vs. outcomes. Behaviorally, children with depression demonstrate abnormal processing of reward magnitudes (Forbes et al., 2007; Guyer et al., 2006). Forbes et al. (2006) found that youth with depression exhibited differential neural response to reward as a function of reward phase and magnitude in the OFC in particular. During reward anticipation, youth with depression showed increased activity in the left superior OFC, particularly in response to low-magnitude rewards. However, the depressed youth showed decreased responses in the right

inferior OFC, especially in response to high-magnitude reward. During reward outcome, depressed youth showed OFC deactivation in responses to small magnitude rewards or losses. Following high-magnitude rewards, depressed youth had increase activation in the inferior OFC. Given these complex associations between depression and neural response as a function of reward phase and magnitude, it would be important to use a task that allows for the separation of these constructs.

Across the reward and depression literature, the ways in which depression is measured, as well as the sample characteristics, vary greatly. This may contribute to the inconsistencies in findings regarding depression and reward-related neural activation, especially for findings relating to the sub-regions of the PFC. Studies use a wide range of techniques to measure depression, including self-report measures of depressive and anhedonic symptoms, using symptom count vs. symptom severity vs. diagnoses of depression, and inclusion/exclusion of current or past depression. For instance, inclusion criteria vary between meta-analyses, with some excluding individuals with remitted depression (Müller et al., 2017) while others do not (Ng et al., 2018). Regarding sample characteristics, empirical studies sometimes pull from community samples, while others recruit patients in clinics. Age is another factor that greatly varies across the empirical literature, as some studies recruit solely adults, solely youth, or a mix of both. It may be possible that children, adolescents, and adults with depression demonstrate different neural responses to reward (Somerville, Jones, & Casey, 2010). Future work should attend to how depression is measured and which samples are used when replicating findings.

## 5.4 Strengths and Limitations

The current study benefitted from a large sample size and a well-validated measure of reward processing. While the use of CYF reports to characterize ELS may limit our ability to speak to the influences of timing, duration, and severity of exposure, this use of a prospective measure may be an advantage over the more often utilized self-reported retrospective measures of child maltreatment. Recent work has found that compared to prospective reports of child maltreatment, retrospectively reported ELS relate more strongly to subjectively assessed outcomes and less strongly to objectively assessed outcomes (Newbury et al., 2018; Reuben et al., 2016). This suggests a reporting bias in individuals who remember or disclose child maltreatment. It may be possible that previous work using self-report measures to distinguish between adversity exposed vs. non-exposed groups may be overestimating their findings. It may also be possible however, that the current study underestimated the effects, as child maltreatment often goes underreported (Sege & Flaherty, 2008).

The current study presented with a few notable limitations. First, in terms of our measure of depression, the sample used in the current study reported relatively low depressive symptoms overall. This may have limited our ability to detect an association between alterations in brain activity and depression. Second, the participants of this study were all men. Epidemiological studies consistently find that, from adolescence through adulthood, women are at greater risk for developing depression than men are, with a female to male ratio of approximately 2:1 (Kessler, 1994; Kessler, Avenevoli, & Merikangas, 2001). Further, research has shown that across countries and ethnic groups, women report higher levels of depression than men do (Van de Velde, Bracke, & Levecque, 2010). This may be one factor that contributed to low depressive symptoms in our sample. Several biological processes and psychosocial events have been posited to play a role in

this gender difference of depression, such as genetic vulnerability, fluctuations in sex hormones, sociocultural roles, coping style, and disadvantaged social status (Noble, 2005; Piccinelli & Wilkinson, 2000). Moreover, socioeconomic and family-related factors have been shown to moderate the relation between gender and depression (Van de Velde et al., 2010).

Third, the current study did not account for potential moderating factors that could have influenced our results, such as poverty and its related stressors, interpersonal factors, and exposure to recent life stress. About two-fifths of the participants in the original PYS sample were from families on welfare, and about two-fifths lived with a single parent. Previous work indicates that, compared to their more economically advantaged counterparts, individuals exposed to childhood poverty are more likely to be exposed to additional environmental stressors (e.g. family turmoil, less social support, neighborhood violence, etc.) (Evans & English, 2018). Moreover, research investigating the effects of childhood adversity finds that individuals exposed to multiple risk factors, as opposed to a single exposure, are at greater risk of developing negative mental health outcomes (Evans, Li, & Whipple, 2013). The current study did not control for exposure to poverty and related stressors that accompany such exposure. Future work using the PYS dataset could include these measures in the analyses, as it may be important to consider additional risk factors that may increase the risk for depression. Importantly, interpersonal factors may serve to protect against the development of depression following ELS exposure. For instance, one study of 513 African American youth found that increased perceived neighborhood fear was associated with greater depressive symptoms (Assari, Smith, Caldwell, & Zimmerman, 2015). However, higher levels of perceived maternal support significantly predicted lower depressive symptoms among the men in the sample. A separate study of 368 adolescents found that the association between interpersonal stress and depressive symptoms was stronger for adolescents high on brooding



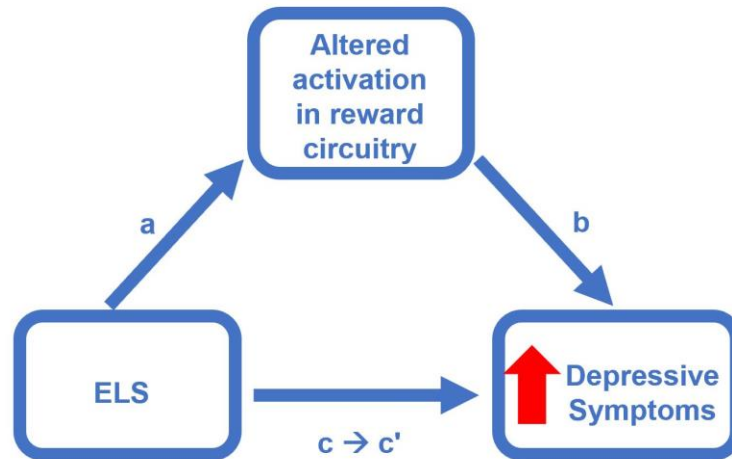
compared to low on brooding (Bastin, Mezulis, Ahles, Raes, & Bijttebier, 2015). Moreover, girls high on co-rumination with peers and boys low on co-rumination with peers demonstrated stronger associations between interpersonal stress and depressive symptoms. It may be important to consider such interpersonal factors as moderators in future work. Finally, given that the participants in our sample were adults, exposure to recent life stress may be another moderating factor. Previous work has found that compared to healthy controls, adults with MDD demonstrated a positive correlation between perceived levels of recent and chronic life stress and greater mPFC activation when processing rewards (Kumar et al., 2015). Moreover, young adults with a history of child maltreatment and greater levels of recent life stress exhibited increased reward-related functional connectivity between the VS and mPFC, and this pattern of connectivity was associated with greater depressive symptoms (Hanson, Knodt, Brigidi, & Hariri, 2018). Taken together, there are several risk and protective factors that should be considered in future work to better understand the impact of ELS exposure on reward-related circuitry and risk for later depression.

## **5.5 Future Directions and Conclusion**

Given the well-supported link between ELS exposure, such as child maltreatment, and the development of later depression, it is imperative to identify mechanisms underlying this association. This is particularly important, as individuals with a history of child maltreatment are often more resistant to treatments for depression (Nanni et al., 2012; Williams et al., 2016). In contrast to our predictions, the current study did not find significant associations between child maltreatment, reward-related neural functioning, and depressive symptoms. There are several differences between the current study and previous work that may begin to explain our inability to

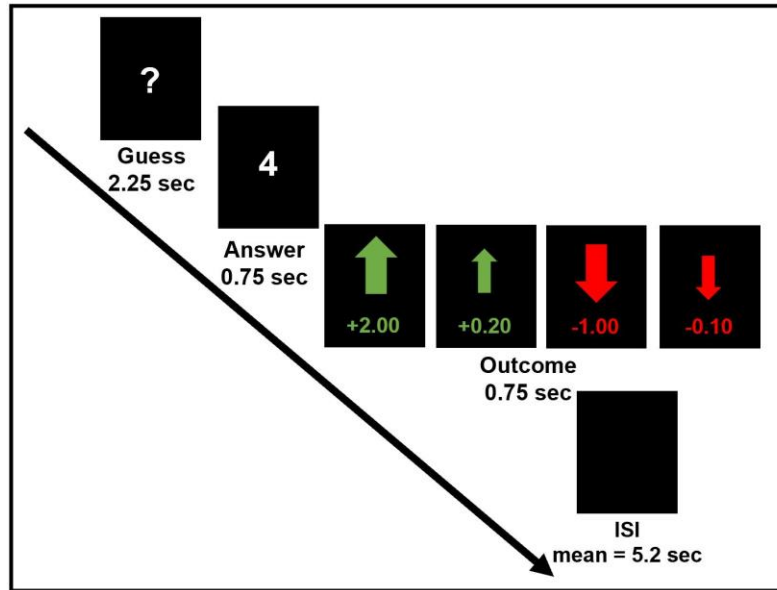
detect significant associations. For instance, in both ELS and depression research independently, neural responses to reward have been shown to differ as a function of reward phase and reward magnitude. Furthermore, there are several inconsistencies in previous literature that still need to be addressed in future work. Regarding neuroimaging findings, both ELS and depression relate to VS deactivation in reward processing tasks, but findings in the sub-regions of the PFC are less consistent. Future work should examine these regions more closely. Moreover, the ways in which ELS are defined and measured greatly differ across studies. Similarly, in studies examining depression and reward processing, depression is characterized in a variety of different ways. It would be beneficial to replicate results more closely to better understand the relations between ELS, the brain, and depression.

## Appendix A



**Figure 1. Hypotheses**

1) ELS will be associated with greater depressive symptoms (path c). 2) Compared to participants without a history of child maltreatment, participants exposed to child maltreatment will have altered functional activation in the reward mask (path a). 3) Altered functional activation in the reward mask will be associated with greater depressive symptoms (path b). 4) There will be an indirect effect of altered activation in the reward mask during the reward processing task on the association between ELS and depressive symptoms (path c').



**Figure 2. fMRI Task Design**

During each trial of the task, the participants had 2.25 seconds to guess, through button press, whether the value of a visually presented card with a possible value of 1–9 was higher or lower than 5. After a choice was made, the “actual” numerical value of the card was presented for 0.75 seconds. Outcome feedback was presented for 0.75 seconds, and a jittered inter-trial interval was presented (mean = 5.2 seconds).

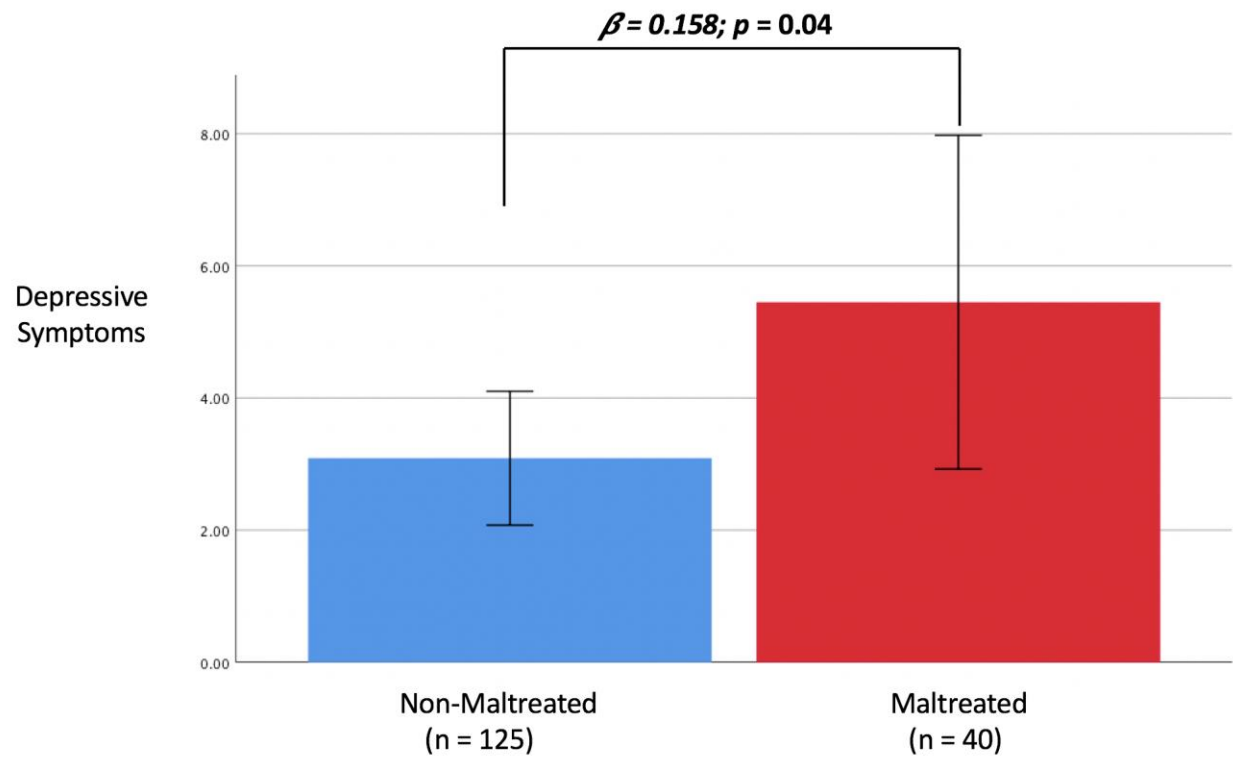


Figure 3. ELS and Depressive Symptoms



Figure 4. OFC Cluster

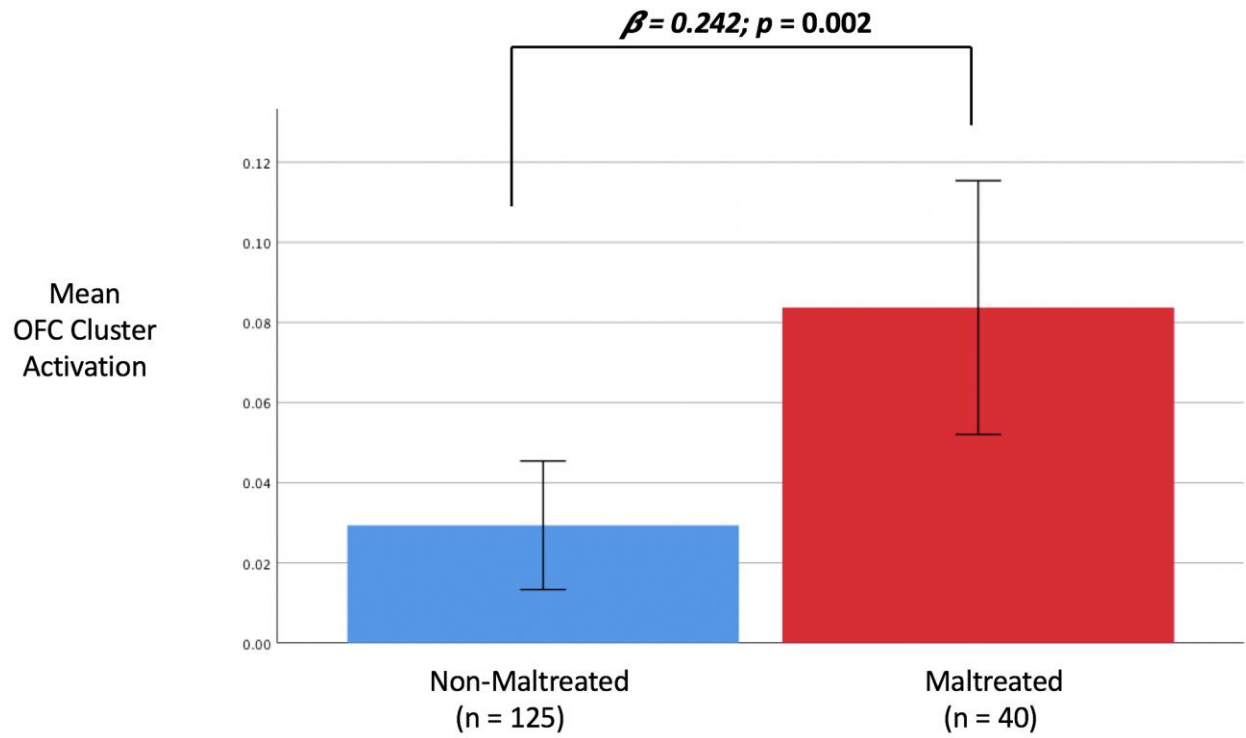


Figure 5. ELS and OFC Cluster

Table 1. Means, Standard Deviations, and Comparison Statistics for Study Variables by Group

Variable	Maltreated Group (n = 40)		Non-Maltreated Group (n = 125)		Comparison Statistic
	M/%	SD	M/%	SD	
Age	32.87	3.25	32.56	3.74	$t(163) = -0.466$ $p = 0.64$
Race (Black/other)	67.5%	---	66.4%	---	$\chi^2(1) = 0.017$ $p = 0.898$
Depression DASS Score	5.45	7.89	3.09	5.72	$\beta = 0.158$ $SE = 6.34$ $p = 0.044$

**Table 2. Clusters Above Trend Threshold, Win > Loss (Exploratory,  $p=.01$ ,  $k=50$ )**

Brain Region	Cluster Size (Voxels)	Peak Coordinates (MNI)			Max t
		X	Y	Z	
Orbitofrontal Cortex	54	+16	+36	-18	-2.82

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